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Dielectric Contrast Between Normal and Tumor Ex-Vivo Human Liver Tissue

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ABSTRACT Microwave ablation (MWA) is a promising treatment option for patients suffering from liver cancer utilizing electromagnetic wave heating within the targeted tissue at microwave frequencies. Knowledge about the dielectric properties of the targeted tissues is essential for the design of recent MWA systems by including treatment monitoring possibilities. This work focuses on the evaluation of the patient-specific dielectric contrast between healthy and diseased liver parts at discrete frequencies at 2.45 GHz and 5.8 GHz, as well as a broadband data analysis. Measurements yield a frequency-dependent dielectric contrast with local maxima for each patient. Due to large variations between the dielectric properties of the patients, the need for individual thresholds can be derived to distinguish between healthy and malignant tissue.

INDEX TERMS Dielectric properties of liver, microwave ablation, tumor tissue.

I. INTRODUCTION

The use of microwave technologies and techniques for medical applications leads to novel methods for diagnostics and treatment options. By increasing the frequency up to the gigahertz regime, the propagating electromagnetic (EM) waves interact with the targeted tissue in a contact-less and nondestructive way. For the development and optimization of advanced microwave devices, the knowledge about dielectric properties of human tissue is essential. Regarding diagnostic methods, the detection of solid tumors is a possible application where microwave technology could be an adequate complement to existing imaging modalities such as radiography, Computer Tomography (CT), Ultrasound (US) and Magnetic Resonance Imaging (MRI). For breast cancer detection, the non-ionizing microwave imaging concept shows promising results and could be used for preventive examinations of women [1], [2]. But also as treatment monitoring tool for microwave ablation (MWA) therapy, microwave tomography could be a suitable candidate [3]. MWA is a minimally invasive technique performed under imaging guidance with the main goal to eradicate malignancies plus a safety margin of 5 mm via heat. The treatment option is commonly used for hepatic tumors such as hepatocellular carcinoma (HCC), which is the second most common cause of cancer-related mortality in the world [4]. For a considerable large number of primary and secondary liver cancers, the surgical resection is not possible [5]. Consequently, minimal-invasive interventional approaches could be applied. Beside MWA, alternative treatment options are radiofrequency ablation (RFA), laser-induced-thermotherapy (LITT), cryoablation, transarterial chemoembolization, and stereotactic radiotherapy [6]. Advantages of MWA compared to other methods are higher ablation volumes in a shorter treatment duration and a reduced susceptibility to the heat-sink effect. However, the demand for treatment monitoring tools for MWA to improve existing systems is high [7]. Beside microwave tomography as treatment monitoring tool, advanced MWA applicators were proposed in [8]–[10]. Those devices are able to measure the permittivity of the surrounding tissue to detect changes of electromagnetic properties due to tumor-healthy tissue boundaries. For this reason, a-priori knowledge about the dielectric properties of tumor and healthy tissue is of particular interest for the design and optimization of novel microwave applicators. Furthermore, temperature induced effects on the permittivity could be monitored to enable a treatment feedback for the practicing radiologist. With increasing temperature, the permittivity of tissue decreases. At very high temperatures over 90 °C such as it occurs during microwave ablation treatments, the dielectric

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properties drop dramatically and continue to decrease with time of exposure [11], [12].

Various studies that investigate dielectric properties of human tissues were conducted. The majority of measurements were performed with ex-vivo tissue samples due to challenging establishment of suitable protocols for in-vivo measurements. In [13], a comprehensive study on the dielectric properties of several biological tissues in the frequency range from 10 Hz to 20 GHz is presented and further processed by a parametric model in [14]. The complex permittivity of liver cancer tissue for the lower microwave frequency range from 50 MHz to 900 MHz was investigated in [15]. In [16], the dielectric properties of human liver were characterized including samples of primary hepatocellular carcinoma, metastatic colorectal carcinoma, and normal tissue over the frequency range from 0.3 GHz to 3 GHz. To meet the demand of knowledge about higher frequency dispersion behavior of liver tissue, the characterization of human normal, malignant and cirrohotic liver tissue up to 20 GHz is presented in [17]. The proposed study included six patients with either HCC or hepatic metastases who underwent hepatic resection surgeries. Beside the measurements of freshly excised ex-vivo liver samples, the complex permittivity of in-vivo liver was also determined. The collected data was evaluated at two single-frequency points at 915 MHz and 2.45 GHz that are commonly used for MWA devices. Moreover, a broadband data analysis was conducted by fitting the ex-vivo measurement data to a single-pole Cole-Cole model. In-vivo liver data could not be represented by a Cole-Cole model, and further, shows an unexpected dispersion trend over 15 GHz. In [18], variations in dielectric properties of malignant and healthy human liver tissues of six patients were examined in the frequency range between 0.1 GHz and 5 GHz.The study comprises an analysis of the permittivity data per patient with the focus on a comparison of the data from different tumor types and a more in-depth discussion about corresponding underlying pathological states of tissue. Furthermore, an analysis of the more recent data from [18] compared to older published data yields that the dielectric properties reported in [17] are generally on higher side compared to all other reported values.

In this work, the complex permittivity of *ex-vivo* human liver samples from hepatic resections is measured including normal and malignant tissue parts from 0.5 MHz to 26.5 GHz. In contrast to previously mentioned studies, the data analysis is focused on the patient-specific dielectric contrast between normal and diseased tissue parts of liver samples. Based on these results, sensitivity requirements on novel microwave devices for hepatic cancer detection can be derived. In Section II, the study procedure and measurement setup is described. Further, the concept is presented how the permittivity data is evaluated and analyzed. The single-frequency and broadband dielectric contrast results are shown and discussed in Section III. Finally, the work is concluded in Section IV.

II. MATERIALS AND METHODS

The dielectric contrast of normal and malignant liver tissue per patient is of particular importance to verify the feasibility of microwave-based hepatic tumor detection systems. Therefore, dielectric measurements of native, freshly excised human liver samples containing healthy and diseased parts from hepatic resection surgeries at J. W. Goethe- University Hospital Frankfurt, Germany, were performed. For the experiments involving the use of human subjects, an ethical approval was obtained from the ethics committee of the J. W. Goethe- University Hospital. The samples were transported from the operating room to the pathology to cut the tissue into slices and mark healthy and diseased tissue parts. The prepared samples were then transported to the measurement laboratories at the Institute of Diagnostic and Interventional Radiology (IDIR). A non-sealed petri dish within a polystyrene box without additional preservative material was used for transportation. The total time from the resection of the liver sample to the first measurement was less than one hour. Patients with contagious liver diseases were not included in the study.

A. MEASUREMENT SETUP

The microwave measurement system consists of a portable vector network analyzer (PXI M9375A, Keysight Technologies) suitable for measurements up to 26.5 GHz and the commercial Slim Form probe (85070E Dielectric Probe Kit, Keysight Technologies) based on an open-ended coaxial structure with an outer diameter of 2.16 mm. The setup is shown in Fig 1(a). Generally, open-ended coaxial probes are widely used for the characterization of dielectric properties from biological tissues [19], [20]. The coaxial probe generates a quasi-static capacitor-like field whose interrogation can be directly correlated to the dielectric properties of the surrounding Material under test (MUT). The region close to the open end of the probe has a higher influence on the resulting measured permittivity compared to regions farther away from the tip. For this reason, the aim for sample preparation is to obtain samples that are as homogeneous as possible within the sensing area of the probe. To ensure a complete electric field absorption in the MUT, the minimum thickness of all tissue samples was 5 mm. Since fringing fields around the coaxial probe are neglectable small, the sensing area is limited to te region where the probe tip touches the MUT. An example of a liver sample with healthy and tumor tissue parts is given in Fig. 1 (b) and (c). The coaxial probe was connected to the VNA with a 90° angled adapter to provide a preferably stable phase condition during the measurements. Furthermore, the setup included mechanical components. An elevating platform was placed on a digital balance to position the MUT right under the dielectric probe. With this, a repeatable pressure for each measurement sample was obtained. The dielectric properties of the MUT were extracted from one-port reflection measurements by applying a calibration procedure that directly maps the measured reflection

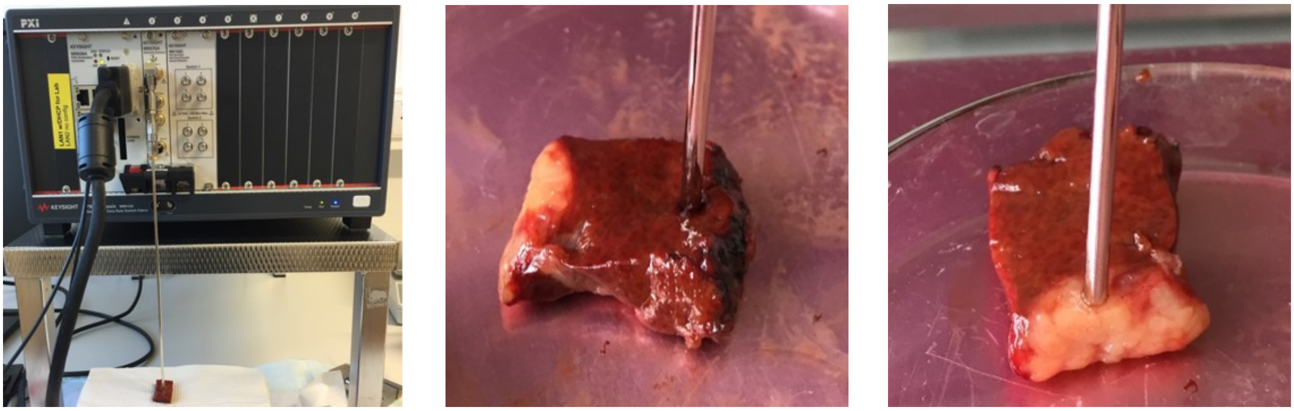

FIGURE 1. (a) Measurement setup consisting of VNA and dielectric probe, example of liver sample including (b) healthy and (c) diseased tissue parts.

coefficient to the complex permittivity plane that was extensively investigated in literature, for example in [21], [22]. The measurements were controlled by a routine in Matlab (The Mathworks Inc.) that guides the user through the calibration, initiates reflection measurements, and monitors the extracted permittivity values of the MUT in real-time. The dielectric probe is calibrated with the standard loads, namely deionized water (DIW), short, and open. Reflection measurements of the coaxial probe inserted in DIW, loaded with a metallic device that is part of the Dielectric Probe Kit, and surrounded by air were conducted. By knowing the complex permittivity values of these standard loads, the bilinear relation between the measured reflection coefficient and permittivity of the MUT can be solved. The accuracy of the applied calibration procedure and proposed measurement system yields a measurement bias within 5 % [23]. The dielectric measurements were conducted in the frequency range from 500 MHz to 26.5 GHz with 2001 equidistantly distributed measurements points and an IF bandwidth of 100 Hz. One measurement took around 50 s. In order to ensure reproducibility of the procedure, two consecutive measurements were performed for each location of the dielectric probe on the sample. For further analysis, the average value of the two consecutive measurements corresponds to one measurement, since they practically overlap. All measurements were performed at an ambient temperature of 21 °C±1 °C. The drift of the calibration with time was evaluated by measuring the permittivity of the reference liquid DIW before and after the tissue sample measurements of each patient. For the real part of the relative permittivity ε_r', the drift is below 1.3 % along the whole spectrum. The measurements of the imaginary part ε_r'' yield a mean drift of 12.3 % for the frequency range below 2 GHz and above that frequency, the drift decreased to 1 %.

B. DATA ANALYSIS

The dielectric properties of biological tissue are mainly characterized by polarization mechanisms. In the frequency range from 0.5 GHz to 26.5 GHz, the dominant polarization mechanism is the dipolar orientation of water molecules. The loss mechanisms in tissue lead to a complex form of the relative permittivity ε_r^*

$$\varepsilon_r^* = \varepsilon_r' - j\varepsilon_r''. \tag{1}$$

The differences between the permittivity of normal and malignant tissue are evaluated at distinct frequencies as well as along the whole frequency spectrum for each patient. For the analysis, 2.45 GHz as widely used operation frequency for MWA systems is considered. Further, we evaluated differences at 5.8 GHz that is located within the next higher ISM band and could be used to realize higher frequency ablation devices. For the broadband analysis of the dielectric contrast between the malignant and normal tissue parts for each patient the real and imaginary part of the measured permittivity data is taken into account. Hence, we define the dielectric contrast Δ as

$$\Delta = \left\| \frac{\varepsilon_{\text{Tumor}}^* - \varepsilon_{\text{Normal}}^*}{\varepsilon_{\text{Normal}}^*} \right\| \tag{2}$$

TABLE 1. Number of measurements for ex-vivo human liver samples.

No.	Tumor	Normal	Histology: Tumor	Histology: Normal
1	5	4	HCC	moderate steatosis
2	9	8	metastasis breast cancer	minor steatosis
3	8	8	HCC	moderate steatosis
4	6	6	metastasis colon cancer	minor steatosis
5	2	7	HCC	minor steatosis
total	30	33		

III. MEASUREMENT RESULTS

Within the proposed study, measurements of liver samples from five patients were conducted. Depending on the respected sample size, 2-9 locations were measured on normal and malignant tissue parts. In total, 30 measurement

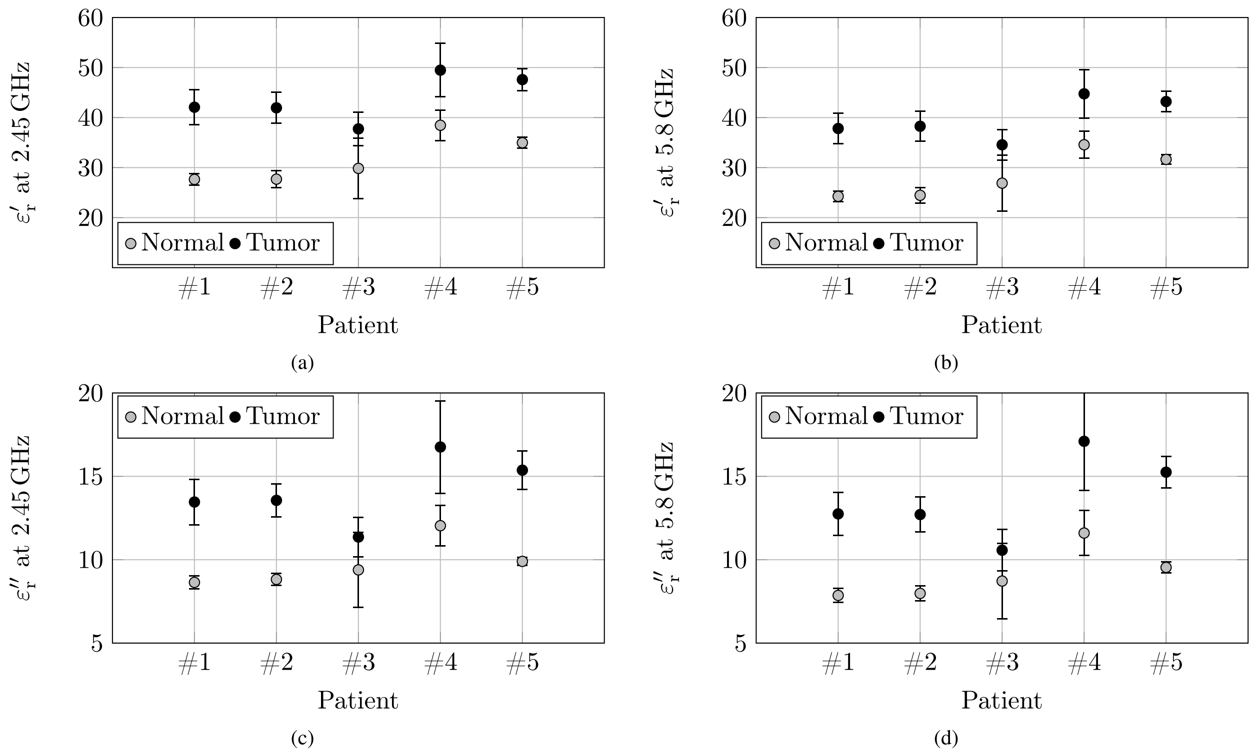

FIGURE 2. **Mean value and standard deviation from complex permittivity of normal and tumor measurements per patient at (a), (c)** 2.45 GHz **and (b), (d)** 5.8 GHz**.**

points in tumor tissue and 33 measurements in normal tissue were included in the study. Measurements of cirrhotic and necrotic liver were not included in the study. According to the pathological findings, all patients in the study suffered from a fatty liver. A summary of the measurement points and histology of the resected liver samples including the degree of steatosis is given in Table 1. In the following, the patient-specific dielectric contrast is evaluated at two single frequencies, 2.45 GHz and 5.8 GHz, and over the frequency spectrum from 0.5 GHz to 26.5 GHz.

A. SINGLE-FREQUENCY DIELECTRIC CONTRAST

Figure 2 shows the mean value and standard deviation of the real and imaginary part of the permittivity for each patient at 2.45 GHz and 5.8 GHz. The permittivity trends observed for 2.45 GHz and 5.8 GHz are very similar. Generally, the difference between normal and malignant measurement points are higher compared to the corresponding standard variations of the measurements. That indicates a possible discrimination between healthy and diseased tissue parts per patient. Only patient 3 exhibits an exceptional large standard deviation of the measurements in normal tissue. A possible explanation could be the presence of tumor cells within the tissue stated as healthy. For all other patients, the standard variation of normal measurements is smaller compared to tumor measurements. This supports the assumption that liver presents a homogeneous tissue structure compared to other tissue parts. The determination of a general threshold value over all patients to distinguish between healthy and diseased tissue is not possible due to the large variations of permittivity values from patient to patient. Therefore, measurements of the actual patient-specific dielectric contrast is needed for the detection of tumors with microwave imaging devices.

The permittivity difference between normal and malignant tissue samples ranges from 20.9 % to 34.3 % for the real part ε_r' and 17.3 % to 35.8 % for the imaginary part ε_r''. Those values are comparable to the data reported in [17] where the relative permittivity and the effective conductivity of malignant tissue at 2.45 GHz were found to be 20 % and 18 % higher than normal tissue, respectively. The slightly larger difference between the mean dielectric properties of normal and tumor tissue from this study can be attributed to the widespread fatty liver samples.

B. BROADBAND DIELECTRIC CONTRAST

The dielectric contrast Δ according to Eq. (2) is determined for each patient. Therefore, we used the mean value of the measured complex permittivity of normal and tumor tissue, respectively. As a result, five curves are generated that depict the contrast Δ in % as a function of frequency in Fig. 3. It can be observed that the dielectric contrast presents a very high variation for different patients. While the maximum dielectric contrast of patient 3 is 28.9 %, patient 2 shows a maximum dielectric contrast of 60.9 %. The patient specific dielectric contrast exhibits a frequency dependency with a maximum at 11.37 GHz, 12.56 GHz, 11.91 GHz, 9.24 GHz, and 7.85 GHz

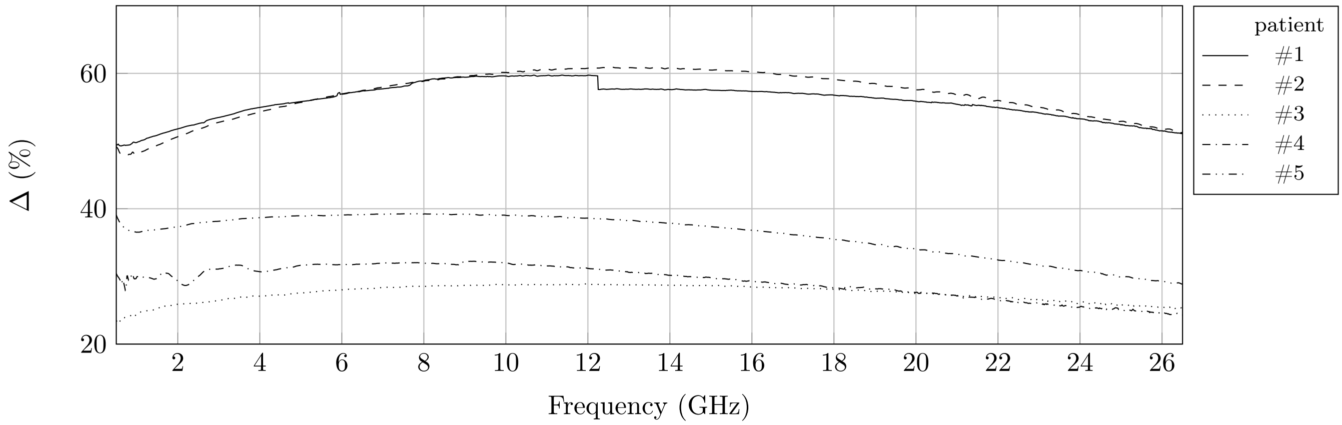

FIGURE 3. Dielectric contrast Δ between normal and tumor tissue as a function of frequency for all five patients.

for patients 1, 2, 3, 4, and 5, respectively. The patients can be separated in two groups representing a high dielectric contrast above 50 % and medium dielectric contrast below this value. Due to the limited number of patients, no relation between primary or secondary cancer type and the dielectric contrast can be observed.

Possible physiological explanations for the increased dielectric properties of tumor compared to normal tissue are a higher sodium and water content of tumor cells [18]. The fact that we observe a frequency where the dielectric contrast reaches a local maximum indicates the presence of a certain relaxation process in tissue that might be related to the increased water content in tumor cells. Regarding the sensitivity requirements for treatment monitoring tools utilizing microwave techniques, the results reveal a certain frequency range between 8 GHz to 12 GHz with maximum dielectric contrasts. However, the question if the frequency range is also optimal for the realization of those devices must be further investigated. Due to the physical limitations of electromagnetic field penetrations with increasing frequency, sensing devices utilizing the proposed frequency range would have very limited penetration depths.

IV. CONCLUSION

Permittivity measurement in the frequency range between 0.5 GHz to 26.5 GHz of freshly excised human liver cancer samples from five patients were performed. The data analysis focused on the evaluation of the patient-specific dielectric contrast between healthy and diseased liver tissue at discrete frequencies at 2.45 GHz and 5.8 GHz and over the whole measured frequency spectrum.

The evaluation of patient-specific dielectric contrasts yielded a high variation between the patients with maximum values between 28.9 % and 60.9 %. The presence of a local maximum in the range of the relaxation frequency of the measured permittivity is an evidence that dipolar polarization mechanisms mainly attribute to the differences between normal and tumor tissues in liver. Further, the measured dielectric contrast were larger compared to the variance of each sample. As a result, the discrimination between healthy and diseased tissue parts would be possible by measuring patient-specific permittivity values. In particular, advanced MWA systems with sensing capabilities and microwave tomography systems could benefit from these findings.

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